Supplementary Figures

Fig. S1

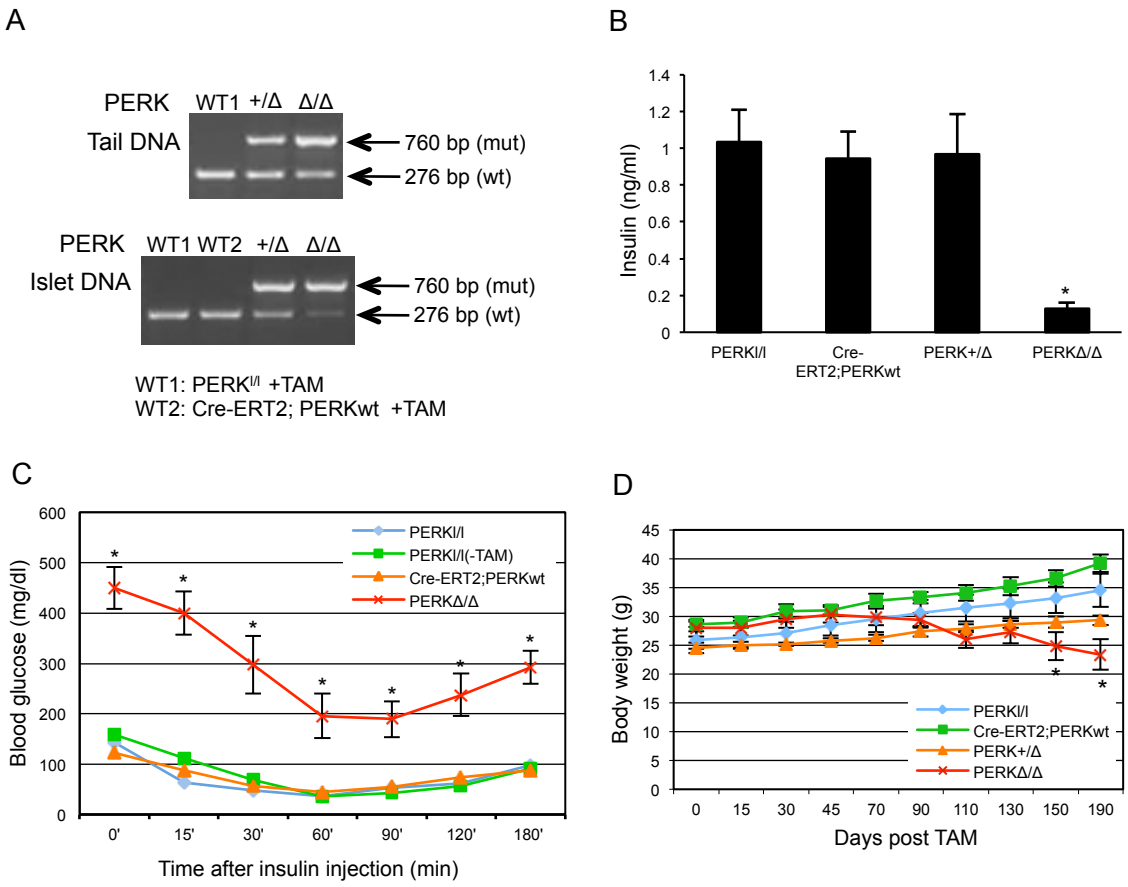

Fig S1. PERK excision at 8 weeks of age leads to reduced plasma insulin. A. Excision PCR analysis using DNA from tail or purified islets isolated from mice of the indicated genotype. **B.** Fed insulin levels in $PERK^{\Delta/\Delta}$ and control groups at 12 weeks post TAM treatment (n=5~7 mice in each case; mean ± SEM). *: $P<0.01$ ($PERK^{\Delta/\Delta}$ vs Cre-ERT2;PERKwt, $PERK^{+/\Delta}$ and $PERK^{l/l}$). **C**. Insulin tolerance test (ITT, n=3~8 mice in each case; mean ± SEM) at 12 weeks post TAM in $PERK^{\Delta/\Delta}$ and control groups. *: $P<0.05$ ($PERK^{\Delta/\Delta}$ vs Cre-ERT2;PERKwt and $PERK^{l/l}$ with or without TAM treatment). **D.** Average weight was measured and plotted every 15 days in all groups after the final TAM administration defined as day "0" (n=5~7 mice in each case; mean ± SEM). *: $P<0.05$ ($PERK^{\Delta/\Delta}$ vs Cre-ERT2;PERKwt and $PERK^{l/l}$).

Fig. S2

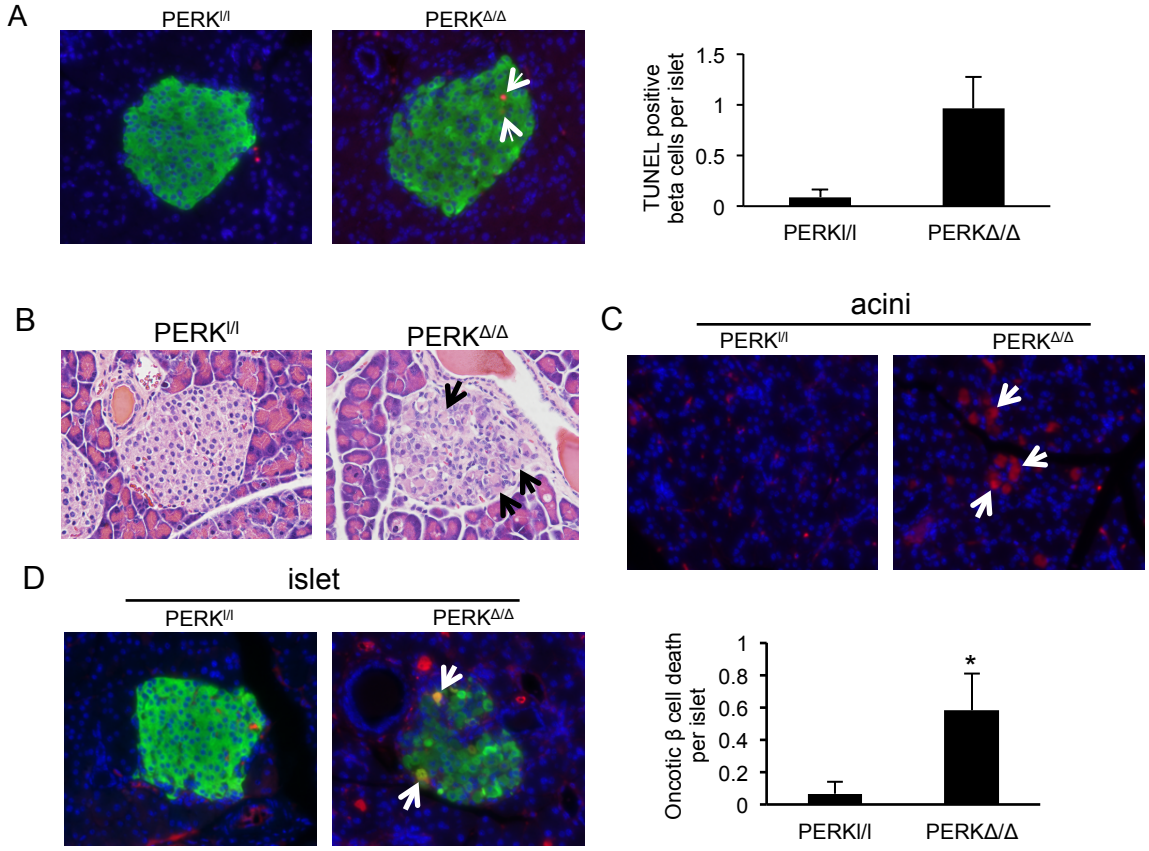

Fig S2. PERK deletion triggers apoptotic β cell death and oncotic acini cell death. A. TUNEL assay was performed using pancreata at 1 week post TAM treatment. Arrows indicate TUNEL, insulin, and DAPI triple positive cells. Insulin (green); TUNEL (red). The graph (20x) represents quantification of TUNEL positive/ insulin positive cells (n=6 mice in each case; mean ± SEM). *: P<0.05 (PERK$^{l/l}$ vs PERK$^{\Delta/\Delta}$). **B**. H&E staining showed the swollen cellular plasma with distorted nuclear as black arrow indicated in the light pink islet (20x) (left). **C & D**. Oncotic acini cell death was assessed by ApoE immunostaining at 3-weeks post-TAM treatment. Arrows indicate ApoE positive acini cells (red) or and ApoE double positive β cells (20x). (n=5 mice in each case; mean ± SEM). *, P<0.05.

Fig. S3

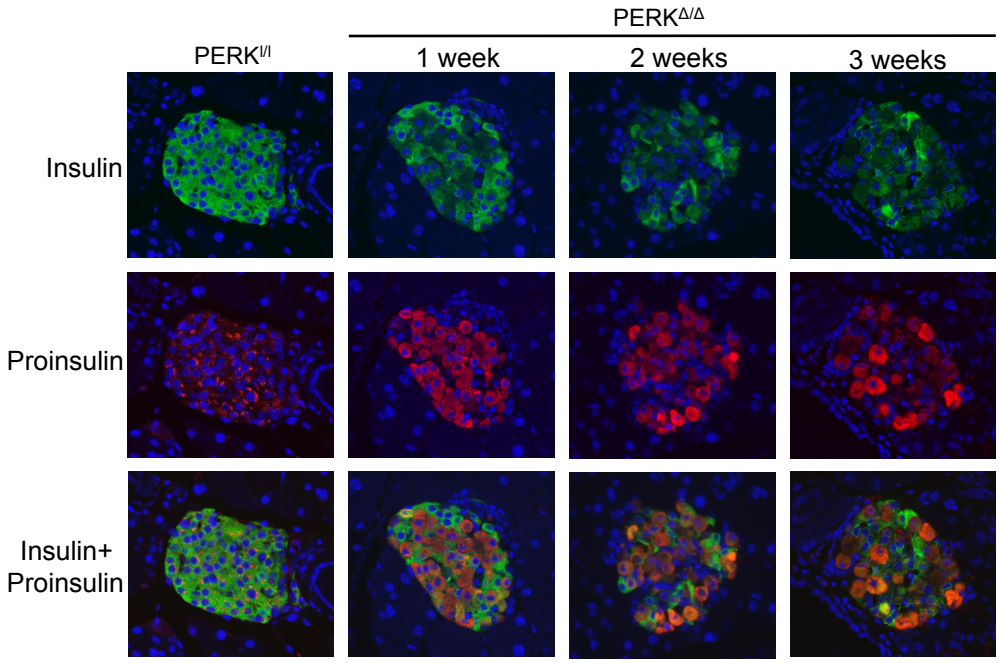

Fig S3. The insulin/proinsulin distribution in PERK$^{l/l}$ versusPERK$^{\Delta/\Delta}$ islets at 1, 2, or 3 weeks post PERK excision. Representative immunofluorescent staining for insulin (green) and proinsulin (red) in β cells (40x).

Fig. S4

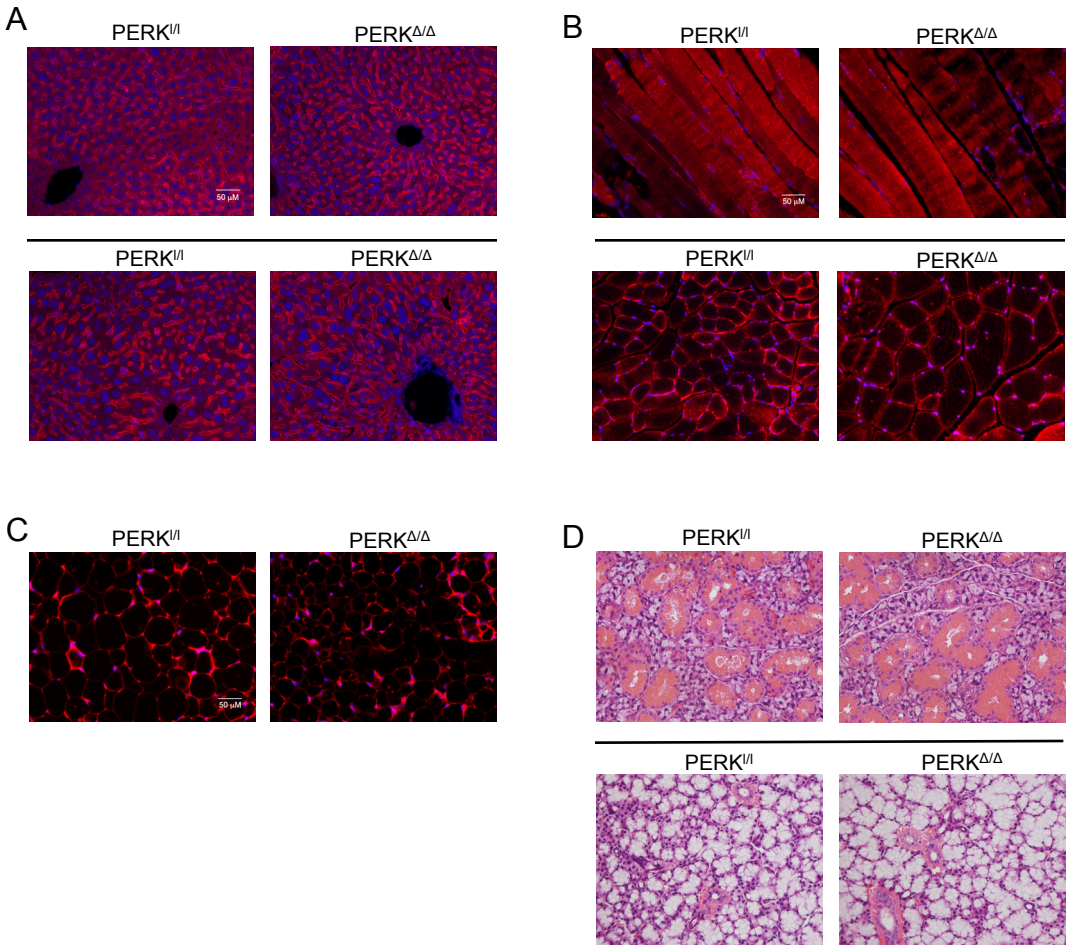

Fig S4. PERK acute excision at 8 weeks of age does not impair glucose transporter membrane targeting in peripheral tissue. A. Paraffin embedded liver section was immuno-stained with Glut2 antibody (red). Top and bottom panels show mice from 3 weeks and 3 months post TAM treatment respectively. **B and C.** Skeletal muscle (B) and white fat sections (C) were from mice at 3 weeks post TAM treatment and immuno-stained with Glut4 antibody (red). Top panel in B, longitudinal section; bottom panel in B, cross section. **D.** Salivary glands from mice at 3 weeks post TAM treatment were stained with hematoxylin-eosin (20x). Top panel, submandibular salivary gland; bottom panel, sublingual salivary gland.

Fig. S5

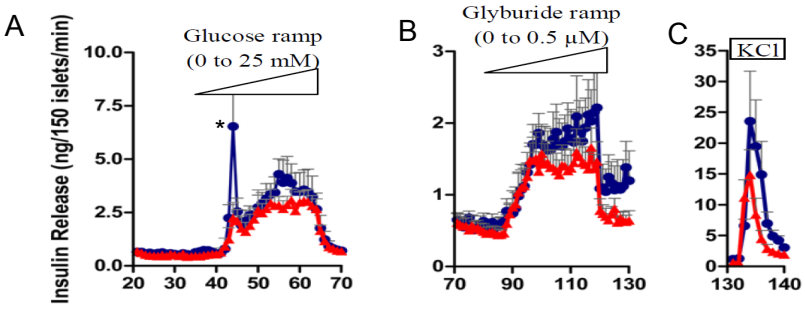

Fig S5. PERK excision at 1 week post TAM administration in young adult mice has little effect on insulin release in vitro. Primary islets were isolated at 1 week post TAM treatment of $PERK^{l/l}$ (blue) and $PERK^{\Delta/\Delta}$ (red) mice and cultured for 3 days. 150 size-matched islets were perfused in response to Glucose ramp (0-25 mM, 0.83 mM/min increment) (**A**) and glyburide ramp (0-0.5 μM, 0.017μM/min increment) (**B**). Finally islets were exposed to potassium chloride (KCl, 30 mM) (**C**) (n=4; mean ± SEM).